DRAFT
INTERACTION PROFILE FOR:
Benzene, Toluene, Ethylbenzene, and Xylenes (BTEX)

U.S. Department of Health and Human Services
Public Health Service
Agency for Toxic Substances and Disease Registry

Public Comment Period Ends September 2, 2002

PREFACE

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) mandates that the Agency for Toxic Substances and Disease Registry (ATSDR) shall assess whether adequate information on health effects is available for the priority hazardous substances. Where such information is not available or under development, ATSDR shall, in cooperation with the National Toxicology Program, initiate a program of research to determine these health effects. The Act further directs that where feasible, ATSDR shall develop methods to determine the health effects of substances in combination with other substances with which they are commonly found. The Food Quality Protection Act (FQPA) of 1996 requires that factors to be considered in establishing, modifying, or revoking tolerances for pesticide chemical residues shall include the available information concerning the cumulative effects of substances that have a common mechanism of toxicity, and combined exposure levels to the substance and other related substances. The FQPA requires that the Administrator of the Environmental Protection Agency consult with the Secretary of the Department of Health and Human Services (which includes ATSDR) in implementing some of the provisions of the act.

To carry out these legislative mandates, ATSDR's Division of Toxicology (DT) has developed and coordinated a mixtures program that includes trend analysis to identify the mixtures most often found in environmental media, *in vivo* and *in vitro* toxicological testing of mixtures, quantitative modeling of joint action, and methodological development for assessment of joint toxicity. These efforts are interrelated. For example, the trend analysis suggests mixtures of concern for which assessments need to be conducted. If data are not available, further research is recommended. The data thus generated often contribute to the design, calibration or validation of the methodology. This pragmatic approach allows identification of pertinent issues and their resolution as well as enhancement of our understanding of the mechanisms of joint toxic action. All the information obtained is thus used to enhance existing or developing methods to assess the joint toxic action of environmental chemicals. Over a number of years, ATSDR scientists in collaboration with mixtures risk assessors and laboratory scientists have developed approaches for the assessment of the joint toxic action of chemical mixtures. As part of the mixtures program a series of documents, Interaction Profiles, are being developed for certain priority mixtures that are of special concern to ATSDR.

The purpose of an Interaction Profile is to evaluate data on the toxicology of the "whole" priority mixture (if available) and on the joint toxic action of the chemicals in the mixture in order to recommend approaches for the exposure-based assessment of the potential hazard to public health. Joint toxic action includes additivity and interactions. A weight-of-evidence approach is commonly used in these documents to evaluate the influence of interactions in the overall toxicity of the mixture. The weight-of-evidence evaluations are qualitative in nature, although ATSDR recognizes that observations of toxicological interactions depend greatly on exposure doses and that some interactions appear to have thresholds. Thus, the interactions are evaluated in a qualitative manner to provide a sense of what influence the interactions may have when they do occur.

The public comment period ends on September 2, 2002. Comments should be sent to:

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PEER REVIEW

A peer review panel was assembled for this profile. The panel consisted of the following members:

1. Dr. Harvey Clewell
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2. Dr. Kannan Krishnan
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All reviewers were selected in conformity with the conditions for peer review specified in Section 104(I)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound. A list of databases reviewed and a list of unpublished documents cited are also included in the administrative record.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the ATSDR.

SUMMARY

Benzene, toluene, ethylbenzene, and xylenes frequently co-occur at hazardous waste sites. Various combinations of these chemicals are among the most frequently found binary mixtures in completed exposure pathways at hazardous waste sites. Media contaminated with these chemicals include air, water, and soil. Contamination of groundwater can result in volatilization into indoor air when the groundwater is used as household water. In addition, contamination of groundwater and subsurface soil can result in migration of these chemicals into basements as soil gas. The purposes of this profile are: (1) to evaluate data on the toxicology of mixtures of benzene, toluene, ethylbenzene, and xylenes (BTEX); (2) to evaluate data on the joint toxic actions (e.g., additive, less-than-additive, or greater-than-additive joint actions) of these chemicals in producing health hazards; and (3) to make recommendations for exposure-based assessments of the potential impact of joint toxic action of the mixture on public health.

No studies are available that directly characterize health hazards and dose-response relationships for exposures to "whole" mixtures of BTEX. Exposure to each of the individual chemicals can produce neurological impairment via parent chemical-induced changes in neuronal membranes. Benzene can additionally cause hematological effects, which may ultimately lead to aplastic anemia and acute myelogenous leukemia, and there is evidence that ethylbenzene is carcinogenic in other tissues. No studies were located that directly examined joint toxic actions of benzene, toluene, ethylbenzene, and xylenes on the nervous system, but additive joint neurotoxic action is plausible for environmental exposures based on predictions from physiologically based pharmacokinetic (PBPK) modeling studies with BTEX and a ternary mixture of its components, and supporting data from neurotoxicity interaction studies of binary component mixtures.

In the absence of data on toxic or carcinogenic responses to the whole mixture, possible health hazards from exposures to BTEX are best assessed using a component-based approach that considers both the shared (neurologic) and unique (hematologic/carcinogenic) critical effects of the constituent chemicals. A hazard index approach that assumes additive joint action and uses ATSDR Minimal Risk Levels (MRLs) and guidance values based on neurological impairment is recommended for exposure-based assessments of possible neurotoxic health hazards from the four components. The possible hematotoxic and carcinogenic hazards of BTEX exposures should be evaluated on the basis of benzene alone due to the causal relationship between the noncancer hematological effects of benzene and the development of leukemia, and the lack of a cancer risk value for ethylbenzene. It therefore is recommended that the cancer unit risk value for benzene be used to jointly assess possible hematotoxic and carcinogenic hazards from exposures to BTEX.

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LIST OF ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienist
AML	acute myelogenous leukemia
ATSDR	Agency for Toxic Substances and Disease Registry
AUC	areas under the blood concentration curves
B	benzene
BEI	biological exposure index
BHIs	biological hazard indexes
BINWOE	binary weight-of-evidence
BTEX	benzene, toluene, ethylbenzene, and xylenes
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CI	confidence interval
cm	centimeters
CYP	cytochrome P-450
DA	dopamine
DBTEX	dichloromethane, benzene, toluene, ethylbenzene, and xylenes
DNA	deoxyribonucleic acid
DOPAC	3,4-dihydroxyphenylacetic acid
DT	Division of Toxicology
E	ethylbenzene
EC_{50}	effective concentration, 50%
EPA	Environmental Protection Agency
FQPA	Food Quality Protection Act
HI	hazard index
5-HIAA	5-hydroxyindoleacetic acid
5-HT	indoleamine serotonin
HVA	homovanillic acid
IARC	International Agency for Research on Cancer
IRIS	Integrated Risk Information System
kg	kilogram
L	liter
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m^3	cubic meters
mg	milligram
mL	milliliter
mm	millimeter
MRI	magnetic resonance imagery
MRL	Minimal Risk Level
NADH	nicotinamide adenine dinucleotide phosphate (reduced form)
NADPH	nicotinamide adenine dinucleotide phosphate (oxidized form)
NE	norepiephrine
NOAEL	no-observed-adverse-effect level
NTP	National Toxicology Program
OPT	olfactory perception thresholds
PBPK	physiologically based pharamacokinetic
ppm	parts per million
RD_{50}	respiratory depression, 50%
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
SC	simulated concentration
SD	standard deviation
STEL	short-term exposure limit
T	toluene
TLV	threshold limit value
TTD	target-organ toxicity dose
TWA	time-weighted average
UDP	uridine-5'-diphosphate
µg	micrograms
µL	microliters
µmol	micromole
U.S.	United States
VMA	vanillylmanelic acid
X	xylenes
,	greater than
$	greater than or equal to
=	equal to
+	less than
#	less than or equal to